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DAFFER MCDANEIL LLP
P.O. BOX 684908
AUSTIN, TX 78768

EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,449	ARCOT, SANTOSH S.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2005* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,5-29,35 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,5-29,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission of RCE filed on April 18, 2005 and the amendment filed on January 31, 2005 have been entered. The claims pending in this application are claims 3, 5-29, 35, and 36. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of amendment filed on January 31, 2004.

Claim Objections

2. Claim 8 is objected to because of the following informalities: "comprise" in lines 2 and 3 should be "comprises". Appropriate correction is required.

3. Claim 27 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim because (iii) of claim 10 only requires that the microspheres of subset of bound probes have an unique fluorescence intensity while at least one fluorescent dye in claim 27 includes more than one fluorescent dye. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 28 recites the limitation "relative amounts of at least two fluorescent dye" in the claim. There is insufficient antecedent basis for this limitation in the claim because (iii) of claim 10 only requires that the microspheres of subset of bound probes have an unique fluorescence intensity. Please clarify.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 10-14, 22, 25, 29, 35, and 36 are rejected under 35 U.S.C. 102(e) as being anticipated by Chee *et al.*, (US Patent No. 6,355,431, priority date: April 20, 1999).

Regarding claim 10, as shown in Figures 7A to 7F, Chee *et al.*, teach: (a) contacting a sample, which is suspected of containing target nucleic acid molecules, with a mixture comprising at least one subset of free probes (ie., a second OLA primer 50) and at least one subset of bound probes (ie., a first OLA primer 45), wherein (i) the free probes comprise two opposing ends, wherein a detectable label is at a first of the two opposing ends (ie., see column

11, last paragraph for the original primer with a fluorescent label) and a nucleotide at a second of two opposing ends, and wherein the free probes further comprising an oligonucleotide having a predetermined nucleotide sequence that is complementary to at least a first portion of the target nucleic acid molecules (see Figure 7B); (ii) the bound probes comprise a microsphere and an oligonucleotide probe wherein the oligonucleotide probes comprise an oligonucleotide at a first end of the oligonucleotide probes having a modifier moiety (ie., amino groups, see column 43, last paragraph bridging to column 44, first paragraph) which is used for coupling the oligonucleotide probe to the microsphere (see column 43) and wherein the oligonucleotide probe further comprises an oligonucleotide having a predetermined nucleotide sequence that is complementary to at least another portion of the target nucleic acid molecules (see Figure 7B); and (iii) the microspheres of the subset of bound probes having an unique spectral address or an unique fluorescence dye which allows one to distinguish the microspheres of the subsets of bound probes from an additional subset of bound probes (see columns 44 and 45) (an additional subset of bound probes is not required to perform the method recited in claim 10); (b) allowing the subset of free probes and the subset of bound probes to hybridize to the target nucleic acid molecules (ie., see Figure 7B); (c) ligating one end of the two opposing ends of the oligonucleotides of the hybridized free probes with one end of the oligonucleotides of the bound probes to provide microsphere-bound ligated products (see Figure 7C); and (d) detecting the presence of microsphere-bound ligated products (see Figures 7D to 7F, and column 6, last paragraph bridging to column 7, first paragraph).

Regarding claims 11 and 12, since the free probes and bound probes bind to different region of the target nucleic acids (see Figures 7A to 7F), Chee *et al.*, teach claims 11 and 12.

Regarding claims 13, 14, and 22, as shown in Figures 7A, 7B, 7C, and 7D, since the second OLA primer 50 (free probe) is 3' of the first OLA primer 45 and 3' -OH of the first OLA primer 45 ligates with phosphate group of the second OLA primer 50 in the presence of a DNA ligase (see attachment in previous office action) to form a 3', 5' phosphodiester bond, Chee *et al.*, teach that the free probe comprises a phosphate at one end of the oligonucleotide of the free probe (5' end of the second OLA primer 50). Since 5' end the second OLA primer 50 (free probe) is used for the ligation reaction and its fluorescence label must be in its 3' end and the first OLA primer 45 with modified moiety comprising an primary amino group (see columns 43 and 44), Chee *et al.*, teach claim 22 because the phrase "which couples the 5' end of the oligonucleotide of the bound probe to a carboxylic acid group on the microsphere" is only considered as an ability of the modified moiety. Since 5' of the first OLA primer 45 has a phosphate, claim 14 is anticipated by Chee *et al.*.

Regarding claims 25 and 29, Chee *et al.*, teach that, after the ligation, the mixtures is added a second enzyme, a polymerase such that the circular probe is amplified in a rolling circle amplification (RCA) assay (see lines 58-65 in column 3). Since, in the assay, ligation and detection are carried out in a single reaction vessel, Chee *et al.*, teach claims 25 and 29.

Regarding claims 35 and 36, since the microsphere includes amino groups including aliphatic and aromatic amines (see lines 65-67 in column 43 and lines 1-3 in column 44), Chee *et al.*, teach the bound probe comprising a microsphere with a modified moiety wherein the modified moiety comprises an primary amino group as recited in claims 35 and 36.

Therefore, Chee *et al.*, teach all limitations recited in claims 10-14, 22, 25, 29, 35, and 36.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 3, 5, 7, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.,* (US 2003/0022182 A1, priority date: February 9, 1996) in view of Chee *et al.,* (April 20, 1999).

Barany *et al.,* teach detection of nucleic acid sequence differences using the ligase detection reaction with addressable arrays.

Regarding claim 3, since Barany *et al.,* teach a method for identifying one or more of a plurality of sequences differing by one or more single-base changes, insertions, deletions, or translocations in a plurality of target nucleotide sequences comprising: providing a sample potentially containing one or more target nucleotide sequences with a plurality of sequence differences; providing a plurality of oligonucleotide probe sets, each set characterized by (a) a first oligonucleotide probe, having a target-specific portion and an addressable array-specific portion, and (b) a second oligonucleotide probe, having a target-specific portion and a detectable reporter label, wherein the oligonucleotide probes in a particular set are suitable for ligation together when hybridized adjacent to one another on a corresponding target nucleotide sequence, but have a mismatch which interferes with such ligation when hybridized to any other nucleotide sequence present in the sample; providing a ligase, blending the sample, the plurality of oligonucleotide probe sets, and the ligase to form a mixture; subjecting the mixture to one or more ligase detection reaction cycles comprising a denaturation treatment, wherein any

hybridized oligonuclecotides are separated from the target nucleotide sequences, and a hybridization treatment, wherein the oligonucleotide probe sets hybridize at adjacent positions in a base-specific manner to their respective target nucleotide sequences, if present in the sample, and ligate to one another to form a ligated product sequence containing (a) the addressable array-specific portion, (b) the target-specific portions connected together, and (c) the detectable reporter label, and, wherein the oligonucleotide probe sets may hybridize to nucleotide sequences in the sample other than their respective target nucleotide sequences but do not ligate together due to a presence of one or more mismatches and individually separate during the denaturation treatment; providing a solid support with different capture oligonucleotides immobilized at particular sites, wherein the capture oligonucleotides have nucleotide sequences complementary to the addressable array-specific portions; contacting the mixture, after said subjecting, with the solid support under conditions effective to hybridize the addressable array-specific portions to the capture oligonucleotides in a base-specific manner, thereby capturing the addressable array-specific portions on the solid support at the site with the complementary capture oligonucleotide; and detecting the reporter labels of ligated product sequences captured to the solid support at particular sites, thereby indicating the presence of one or more target nucleotide sequences in the sample (see page 34, claim 1) and the reporter label is a magnetic probe (see column 7, [0087]), Barany *et al.,* disclose contacting a sample suspected of containing one or more target nucleic acid sequences with one or more subset of free probes (ie., one or more set of the first oligonucleotide probes) and one or more subsets of spectrally-addressable probes (ie., one or more set of the second oligonucleotide probes each labels with a magnetic probe); allowing the one or more subsets of free probes and the one or more subsets of spectrally-addressable probes to hybridize to the one or more target nucleic acid sequences, if present in the sample; ligating

the hybridized free probes with the hybridized spectrally-addressable probes, wherein a free probe hybridized to a target nucleic acid sequence is ligated with a spectrally-addressable probe hybridized to the same target nucleic acid sequence, to provide spectrally-addressable ligated products; and detecting a presence of the spectrally-addressable ligated products, analyzing the target nucleic acid sequences of the spectrally-addressable ligated products, or performing said detecting and said analyzing as recited in claim 3. Since Barany *et al.*, teach one or more target nucleotide sequences with a plurality of sequence differences (see page 34, claim 1), according to the definition in the specification (see page 9), "substantially identical" means that, when used in connection with the phrase nucleotide sequence, "one or more nucleotides at one or more positions of probes in a subset may differ due to one or more substitutions, insertions, deletions, or combinations thereof but can still be distinguished from probes belonging to another subset and can substantially hybridize to the correct position on the target molecule," Barany *et al.*, disclose that the first portions of the first and second target nucleic acids in one or more target nucleic acids sequences recited in claim 3 are distinguishable while the second portions of the first and second target nucleic acids in one or more target nucleic acids sequences recited in claim 3 are substantially identical. Since Barany *et al.*, teach a plurality of oligonucleotide probe sets, each set characterized by a first oligonucleotide probe and a second oligonucleotide (see page 34, claim 1), Barany *et al.*, disclose that a first subset of one or more subsets of spectrally addressable probes (ie., the second oligonucleotide in the first oligonucleotide probe sets) is specific for the first portion of the one or more first target nucleic acid sequences and a second subset of one or subsets of spectrally addressable probes (ie., the second oligonucleotide in the second oligonucleotide probe sets) is specific for the first portion of the one or more second target nucleic acid sequences as recited in claim 3. According to the definition of "substantially

identical" in the specification (see page 9), Barany *et al.*, teach that one or more subsets of free probes (ie., the first oligonucletide probes in a plurality of oligonucleotide probe sets) have substantially identical nucleotide sequence that are specific for the second portion of the one or more first and second target nucleic acid sequences as recited in claim 3.

Regarding claim 5, since Barany *et al.*, teach a method for identifying one or more of a plurality of sequences differing by one or more single-base changes, insertions, deletions, or translocations in a plurality of target nucleotide sequences comprising: providing a sample potentially containing one or more target nucleotide sequences with a plurality of sequence differences; providing a plurality of oligonucleotide probe sets, each set characterized by (a) a first oligonucleotide probe, having a target-specific portion and an addressable array-specific portion, and (b) a second oligonucleotide probe, having a target-specific portion and a detectable reporter label, wherein the oligonucleotide probes in a particular set are suitable for ligation together when hybridized adjacent to one another on a corresponding target nucleotide sequence, but have a mismatch which interferes with such ligation when hybridized to any other nucleotide sequence present in the sample; providing a ligase, blending the sample, the plurality of oligonucleotide probe sets, and the ligase to form a mixture; subjecting the mixture to one or more ligase detection reaction cycles comprising a denaturation treatment, wherein any hybridized oligonuclecotides are separated from the target nucleotide sequences, and a hybridization treatment, wherein the oligonucleotide probe sets hybridize at adjacent positions in a base-specific manner to their respective target nucleotide sequences, if present in the sample, and ligate to one another to form a ligated product sequence containing (a) the addressable array-specific portion, (b) the target-specific portions connected together, and (c) the detectable reporter label, and, wherein the oligonucleotide probe sets may hybridize to nucleotide sequences

in the sample other than their respective target nucleotide sequences but do not ligate together due to a presence of one or more mismatches and individually separate during the denaturation treatment; providing a solid support with different capture oligonucleotides immobilized at particular sites, wherein the capture oligonucleotides have nucleotide sequences complementary to the addressable array-specific portions; contacting the mixture, after said subjecting, with the solid support under conditions effective to hybridize the addressable array-specific portions to the capture oligonucleotides in a base-specific manner, thereby capturing the addressable array-specific portions on the solid support at the site with the complementary capture oligonucleotide; and detecting the reporter labels of ligated product sequences captured to the solid support at particular sites, thereby indicating the presence of one or more target nucleotide sequences in the sample (see page 34, claim 1) and the reporter label is a magnetic probe (see column 7, [0087]), Barany *et al.,* disclose contacting a sample suspected of containing one or more target nucleic acid sequences with one or more subset of free probes (ie., one or more set of the first oligonucleotide probes and one or more subsets of spectrally-addressable bound probes (ie., one or more set of the second oligonucleotide probes); allowing the one or more subsets of free probes and the one or more subsets of spectrally-addressable bound probes to hybridize to the one or more target nucleic acid sequences, if present in the sample; ligating the hybridized free probes with the hybridized spectrally-addressable probes, wherein a free probe hybridized to a target nucleic acid sequence is ligated with a spectrally-addressable probe hybridized to the same target nucleic acid sequence, to provide spectrally-addressable ligated products; and detecting a presence of the spectrally-addressable ligated products, analyzing the target nucleic acid sequences of the spectrally-addressable ligated products, or performing said detecting and said analyzing as recited in claim 5. Since Barany *et al.,* teach one or more target nucleotide

sequences with a plurality of sequence differences (see page 34, claim 1), according to the definition in the specification (see page 9), "substantially identical" means that, when used in connection with the phrase nucleotide sequence, "one or more nucleotides at one or more positions of probes in a subset may differ due to one or more substitutions, insertions, deletions, or combinations thereof but can still be distinguished from probes belonging to another subset and can substantially hybridize to the correct position on the target molecule," Barany *et al.*, disclose that the first portions of the first and second target nucleic acids in one or more target nucleic acids sequences recited in claim 5 are distinguishable while the second portions of the first and second target nucleic acids in one or more target nucleic acids sequences recited in claim 5 are substantially identical. Since Barany *et al.*, teach a plurality of oligonucleotide probe sets, each set characterized by a first oligonucleotide probe and a second oligonucleotide (see page 44, claim 1), Barany *et al.*, disclose that a first subset of one or more subsets of free probes (ie., the first oligonucleotide in the first oligonucleotide probe sets) is specific for the first portion of the one or more first target nucleic acid sequences and a second subset of free probes (ie., the first oligonucleotide in the second oligonucleotide probe sets) is specific for the first portion of the one or more second target nucleic acid sequences as recited in claim 5. According to the definition of "substantially identical" in the specification (see page 9), Barany *et al.*, teach that one subset of spectrally addressable bound probes (ie., the second oligonucletide probes in a plurality of oligonucleotide probe sets) has substantially identical nucleotide sequence that are specific for the second portion of the one or more first and second target nucleic acid sequences as recited in claim 5.

Regarding claim 7, the ligase taught by Barany *et al.,* is considered to be thermostable (see page 34, claim 1) since the ligation reaction is performed in a certain temperature in order to maximize the activity of the ligase.

Regarding claim 9, Barany *et al.,* teach contacting the sample with polymerase chain reaction components and amplifying the one or more target nucleic acid sequences (see Figures 8 and 9).

Barany *et al.,* do not disclose spectrally-addressable bound probes as recited in claim 3. Instead, they teach spectrally-addressable probes (ie., one or more set of the second oligonucleotide probes each labels with a magnetic probe) (see above).

Chee *et al.,* teach that a magnetic probe used for labeling spectrally-addressable probes is a magnetic particle (see column 30, last paragraph bridging to page 31, first paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 3 or claim 5 using spectrally-addressable bound probes in view of the prior art of Barany *et al.,* and Chee *et al.*. One having ordinary skill in the art would have been motivated to do so because the simple substitution of one kind of reporter label (ie., a magnetic probe taught by Barany *et al.,*) from another kind of reporter label (ie., a magnetic particle taught by Chee *et al.,*) during the process of labeling spectrally-addressable probes (producing spectrally-addressable bound probes), in the absence of convincing evidence to the contrary, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the reporter label taught by Barany *et al.,* and the reporter label taught by Chee *et al.,* have been shown to use for labeling spectrally-addressable probes and are exchangeable.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

11. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.,* (May 29, 1996) in view of Chee *et al.,* (April 20, 1999) as applied to claim 3, 5, 7, and 9 above, and further in view of Kwok *et al.,* (US Patent No. 5,945,283, published on August 31, 1999).

The teachings of Barany *et al.,* and Chee *et al.,* have been summarized previously, *supra.*

Barany *et al.,* and Chee *et al.,* do not disclose that the assay is performed in a first and a second reaction vessel, wherein a first portion of the sample is contacted with the first subset of free probes in the first reaction vessel and wherein a second portion of the sample is contacted with the second subset of free probes in the second reaction vessel as recited in claim 6.

Kwok *et al.,* teach to test two nucleic acid samples in separate reaction vessels (see column 5, third paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the assay recited in claim 6 in a first and a second reaction vessel wherein a first portion of the sample is contacted with the first subset of free probes in the first reaction vessel and a second portion of the sample is contacted with the second subset of free probes in the second reaction vessel in view of the prior art of Barany *et*

al., Chee *et al.*, and Kwok *et al.*. One having ordinary skill in the art would have been motivated to do so because Kwok *et al.*, have successfully tested two nucleic acid samples in separate reaction vessels and performing the assay recited in claim 6 in separate reaction vessels would enhance to use a single sample for multiple purposes and save laboratory cost. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to perform the assay recited in claim 6 in separate reaction vessels.

12. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over as applied to Barany *et al.*, (February 9, 1996) in view of Chee *et al.*, (April 20, 1999) as applied to claims 3, 5, 7, and 9 above, and further in view of Church *et al.*, (US Patent No. 6,485,944 B1, filed on March 12, 1999).

The teachings of Barany *et al.*, and Chee *et al.*, have been summarized previously, *supra.*

Barany *et al.*, and Chee *et al.*, do not disclose that each of spectrally-addressable bound probes in the first subset comprise a first amount of at least one fluorescent dye, wherein each of the spectrally-addressable bound probes in the second subset probes in the second subset comprise a second amount of the at least one fluorescent dye, wherein the first amount is different than the second amount, and wherein the first subset and second subset are distinguishable based at least on the first and second amounts as recited in claim 8. However, since Chee *et al.*, teach that a magnetic particle comprises an optical signature such as a fluorescent molecule (see columns 43-45), Barany *et al.*, in view of Chee *et al.*, disclose that spectrally-addressable bound probe (ie., one or more set of the second oligonucleotide probes) each labels with a magnetic probe having a fluorescent dye (see the rejection under 35 USC 103 on claims 3, 5, 7, and 9).

Church *et al.*, teach that, when a first and a second nucleic acid probes are labeled with a first and a second fluorescent dyes, the relative amounts of the first fluorescent dye and the second fluorescent dye are used to detect the amount of a RNA expression in a first RNA-containing nucleic acid population relative to that expressed in a second RNA-containing nucleic acid population (see column 2, fifth paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 8 wherein each of spectrally-addressable bound probes in the first subset comprises a first amount of at least one fluorescent dye, wherein each of the spectrally-addressable bound probes in the second subset probes in the second subset comprises a second amount of the at least one fluorescent dye, wherein the first amount is different than the second amount, and wherein the first subset and second subset are distinguishable based at least on the first and second amounts in view of the prior art of Barany *et al.*, Chee *et al.*, and Church *et al.*. One having ordinary skill in the art would have been motivated to do so because Church *et al.*, have successfully detected relative amount of two nucleic acids using the relative amount of the first fluorescent dye and the second fluorescent dye (see Church *et al.*, column 2, fifth paragraph) and the simple replacement of one well known fluorescence detection method (i.e., the method taught by Barany *et al.* in view of Chee *et al.*,) from another well known fluorescence detection method (i.e., using the relative amount of the first fluorescent dye and the second fluorescent dye by Church *et al..*,) during the process of performing the method recited claim 3 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the fluorescence detection method taught by Barany *et al.*, in view of Chee *et al.*, and the fluorescence detection method taught by Church *et al.*, are functional

equivalent methods which are used for the same purpose (ie., detection of nucleic acid hybridization).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

13. Claims 15-19, 23, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over as applied to Chee *et al.*, (April 20, 1999) as applied to claims 10-14, 22, 25, 29, 35, and 36 above, and further in view of Barany *et al.*, (February 9, 1996).

The teachings of Barany *et al.*, and Chee *et al.*, have been summarized previously, *supra.*

Chee *et al.*, do not disclose that a mixture comprising an additional subset of bound probes that is different from the subset of bound probe recited in claim 10 and an additional subset of free probes that is different from the subset of free probe recited in claim 10 as recited in claims 15-19, 23, and 24.

Barany *et al.*, teach a plurality of oligonucleotide probe sets comprising bound probes and free probes wherein each of the bound probes or the free probes are different in mismatches (see column 34, claim 1) (ie., each of the bound probes or the free probes are substantially identical).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the assay recited in claims 15-19, 23, and 24 wherein the mixture comprises an additional subset of bound probes that is different from the subset of bound probe recited in claim 10 and an additional subset of free probes that is different

from the subset of free probe recited in claim 10 in view of the prior art of Chee *et al.*, and Barany *et al.*. One having ordinary skill in the art would have been motivated to do so because Barany *et al.*, suggest that performing a ligase reaction in the presence of plurality of oligonucleotide probe sets comprising bound probes and free probes would carry out multiplex analyses of complex genetic systems so that a large number of nucleotide sequence differences in a sample are detected at one time (see column 4, [0034]). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to perform a ligase reaction in the presence of plurality of oligonucleotide probe sets comprising bound probes and free probes wherein each of the bound probes or the free probes are different in mismatches.

14. Claims 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over as applied to Chee *et al.*, (April 20, 1999) in view of Barany *et al.*, (February 9, 1996) as applied to claims 10-14, 22, 25, 29, 35, and 36 above, and further in view of Drmanac *et al.*, (US Patent No. 6,383,742 B1, filed on August 15, 1997).

The teachings of Chee *et al.*, and Barany *et al.*, have been summarized previously, *supra.*

Chee *et al.*, and Barany *et al.*, and do not disclose that the detectable label of the subset of free probes differs from the detectable label of the additional subset of free probes as recited in claim 20. However, since Barany *et al.*, teach a plurality of oligonucleotide probe sets comprising bound probes and free probes wherein each of the bound probes or the free probes are different in mismatches, Barany *et al.*, disclose that the bound probes have substantially identical predetermined nucleotide sequence as recited in claim 21.

Drmanac *et al.*, teach to use oligonucleotide probes with different labels for hybridization (see column 3, last paragraph bridging to column 4, first paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the assay recited in claims 20 and 21 wherein the detectable label of the subset of free probes differs from the detectable label of the additional subset of free probes in view of the prior art of Chee *et al.*, Barany *et al.*, and Drmanac *et al.*. One having ordinary skill in the art would have been motivated to do so because Drmanac *et al.*, suggest that the different probes having different labels are multiplexed in a hybridization reaction so that hybridization of the different probes to the target is distinguished (see column 3, last paragraph bridging to column 4, first paragraph). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to perform the assay recited in claims 20 and 21 wherein the detectable label of the subset of free probes differs from the detectable label of the additional subset of free probes.

15. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chee *et al.*, (April 20, 1999) in view of Barany *et al.*, (May 29, 1996) as applied to claim 10-14, 22, 25, 29, 35, and 36 above, and further in view of Kwok *et al.*, (US Patent No. 5,945,283, published on August 31, 1999).

The teachings of Chee *et al.*, and Barany *et al.*, have been summarized previously, *supra*.

Chee *et al.*, and Barany *et al.*, do not disclose that the assay is performed in separate reaction vessel using at least one of the separate reaction vessels for each of the subset of free probes and the additional subset of free probes as recited in claim 26.

Kwok *et al.*, teach to test two nucleic acid samples in separate reaction vessels (see

column 5, third paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the assay recited in claim 26 wherein the assay is performed in separate reaction vessel using at least one of the separate reaction vessels for each of the subset of free probes and the additional subset of free probes in view of the prior art of Chee *et al.*, Barany *et al.*, and Kwok *et al.*. One having ordinary skill in the art would have been motivated to do so because Kwok *et al.*, have successfully tested two nucleic acid samples in separate reaction vessels and performing the assay recited in claim 6 in separate reaction vessels would enhance to use a single sample (ie., the same mixture) for multiple purposes and save laboratory cost. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to perform the assay recited in claim 26 in separate reaction vessels.

16. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over as applied to Chee *et al.*, (April 20, 1999) in view of Barany *et al.*, (February 9, 1996) as applied to claims 10-14, 22, 25, 29, 35, and 36 above, and further in view of Church *et al.*, (US Patent No. 6,485,944 B1, filed on March 12, 1999).

The teachings of Chee *et al.*, and Barany *et al.*, have been summarized previously, *supra.*

Chee *et al.*, and Barany *et al.*, do not disclose that fluorescent intensity of the subset of bound probes is different from fluorescent intensity of the additional subset of bound probes as recited in claim 27. However, since Chee *et al.*, teach that a magnetic particle comprises an optical signature such as a fluorescent molecule (see columns 43-45), Barany *et al.*, in view of Chee *et al.*, teach that spectrally-addressable bound probe (ie., one or more subset of the second

oligonucleotide probes) each labels with a magnetic probe having a fluorescent dye (see the rejection under 35 USC 103 on claims 3, 5, 7, and 9).

Church *et al.*, teach that, when a first mRNA-containing nucleic acid population and a second mRNA-containing nucleic acid population are labeled with a first and a second fluorescent dyes, the intensities of the first fluorescent dye and the second fluorescent dye are used to detect relative expression of a first mRNA-containing nucleic acid population relative to that expressed in a second mRNA-containing nucleic acid population (see column 2, last paragraph bridging to column 3, first paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 27 wherein fluorescent intensity of the subset of bound probes is different from fluorescent intensity of the additional subset of bound probes in view of the prior art of Chee *et al.*, Barany *et al.*, and Church *et al.*. One having ordinary skill in the art would have been motivated to do so because Church *et al.*, have successfully detected relative amount of two nucleic acids by comparing intensities of the first fluorescent dye and the second fluorescent dye (see Church *et al.*, see column 2, last paragraph bridging to column 3, first paragraph) and the simple replacement of one well known fluorescence detection method (i.e., the method taught by Barany *et al.* in view of Chee *et al.*,,) from another well known fluorescence detection method (i.e., using the intensities of the first fluorescent dye and the second fluorescent dye by Church *et al.*.,) during the process of performing the method recited claim 27 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the fluorescence detection method taught by Barany *et al.*, in view of Chee *et al.*, and the fluorescence detection method taught by Church *et al.*, are

functional equivalent methods which are used for the same purpose (ie., detection of nucleic acid hybridization).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

Response to Arguments

17. Applicant's arguments with respect to claims 3, 5-9, 15-21, 23, 24, and 26-28, have been considered but are moot in view of the new ground(s) of rejection. Note that applicant's arguments with respect to the rejection under 35 U.S. C 102 on claims 10-14, 22, 25, 29, 35, and 36 have been address on advisory action mailed on March 3, 2005.

Conclusion

18. No claim is allowed.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (703)872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (571)272-0745.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
June 22, 2005

FRANK LU
PATENT EXAMINER